REMARKS/ARGUMENTS

Claims 3, 4, 8-11, 16 and 19 are in the case. No claim amendments are presented with this paper.

I. THE INTERVIEW

At the outset, the undersigned wishes to acknowledge the interview conducted in this case on December 11, 2008. The interview was attended by the Examiner (Mr. Kosack) and by his supervisor (Mr. Shiao). The courtesies extended by the Examiner and his supervisor were most appreciated. The substance of the interview will be clear from the Interview Summary and the comments presented below.

II. THE OBVIOUSNESS REJECTION

In the Final Action mailed February 8, 2008, claims 1, 3, 4, 6, 8-11, 16 and 19 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Friedlos et al., *J. Med. Chem.* 1997, 1270-1275 in view of Patani et al., *Chem. Rev.* 1996, 3147-3176. In the response filed May 8, 2008, claims 1 and 6 were canceled without prejudice. The obviousness rejection as it was applied to those claims has accordingly been rendered moot.

The remaining claims were amended to cover compounds of formula IIIb as set forth in claim 4. Formula IIIb covers a subset of compounds of formula IIb, in which A and B are bromine and mesylate. For the reasons argued below, it is believed that the invention as now claimed is clearly patentably distinguished over the art of record.

In the Final Action, compounds 12-16 of Friedlos were identified as the closest compounds to those presently claimed. In the Advisory Action issued in reply to the Response filed May 8, 2008, the Office further asserted that:

> "The person of ordinary skill in the art would be knowledgeable enough to not only attempt the unsymmetrical structure of compound 6 of Friedlos et al. in the framework of compounds 12-16 of Friedlos et al., but would from looking at the presented activities, know that not only does using bromine create a [sic] active drug, but one that has a greater activity than the chlorine substituted drugs."

It is applicants' position that one of ordinary skill would not have been motivated to arrive at the presently claimed compounds based on compounds 12-16 or 6 of Friedlos. There is no disclosure or suggestion in Friedlos which would have led a chemist to modify the Friedlos compounds 12-16 or 6 in a way such that the claimed compounds would have been produced or suggested.

With regard to compounds 12-16, one of ordinary skill would not have been motivated to modify those compounds in the manner required to obtain the bromomesylate compounds of formula IIIb as now claimed, as this would have required abandoning the symmetric structure in which both X and Y are the same to move to an asymmetric structure in which X and Y are different. There is no suggestion in Friedlos to do that, and there would have been no motivation on the part of the skilled artisan to effect that modification. Such a structural modification is contrary to the entire disclosure of Friedlos in which it is only compounds in which X and Y are the **same** that **are sufficiently potent**.

The only example of a compound in Friedlos in which X and Y are different is compound 6. However, compound 6 is expressly referenced as **insufficiently potent**

to allow a full data set to be collected (Friedlos, page 1272). This lack of potency of the only compound described in Friedlos having different values for X and Y clearly would have provided no motivation to one of ordinary skill to even explore such asymmetric compounds further, much less with any expectation of viable activity. The data provided for compound 6 leads **away** from the invention now claimed. Absent any such motivation, no *prima facie* case of obviousness is generated in this case.

The Action asserts that replacing the weaker chlorine with bromine in compound 6 would lead to a more potent drug. However, as discussed during the interview, even replacement of a chlorine by a bromine in compound 6 would not result in or suggest a compound of formula IIIb as now claimed. Thus, replacement of a chlorine with a bromine would not be enough - formula IIIb requires X and Y to be *meta* to each other, whereas the corresponding groups for compound 6 are *para* to each other. To move from compound 6 to a compound of formula IIIb would therefore require **TWO** structural modifications rather than one, neither of which are suggested by Friedlos.

It is further noted that replacement of a chlorine with a bromine in either compound 12 or compound 15 would not yield a bromomesylate compound of formula IIIb now claimed. It would only be the replacement of a bromine by a mesylate in compound 13 which would achieve that. However, with regard to the possible replacement of a bromine with a mesylate to move from compound 13 to a bromomesylate compound of the present invention, it is clear that there would have been no motivation for one of ordinary skill, based on Friedlos, to replace a bromine with a mesylate or to substitute a mesylate for any other substituent. Indeed, based on Friedlos, mesylate would be the last substituent to be selected in an attempt to produce

a more active compound. **None** of the compounds described by Friedlos which have mesylate as a value for X or Y are reported as sufficiently potent, whether symmetric or asymmetric in structure. In fact, when the data for compound 4 (in which X and Y are chlorine) is compared to the data for compound 6 (in which one chlorine is replaced by mesylate) and to that for compound 7 (in which both chlorines are replaced by mesylate), the substitutions lead to compounds with poorer activity (see Table 1). In combination, this suggests an "anything but mesylate" approach to modification in order to obtain a more active compound in this system would be derived from Friedlos.

The above-discussed deficiencies of Friedlos are not cured by Patani. Patani merely provides a general teaching relating to bioisosterism in drug design. Patani does nothing to motivate the skilled artisan to move from an active symmetric structure to an asymmetric structure with any expectation of viable activity. In particular, Patani provides no disclosure or suggestion which would have motivated replacing a bromine with a mesylate in compound 13 of Friedlos to yield a bromomesylate compound of formula IIIb to counter the Friedlos teaching away from such a substitution.

The reality is that compound 6 has a very **poor** potency. The IC50 of 3.4 micromolar reported against cell line T79-A3 is well above effective levels. For example, the equivalent IC50 value for compound 1 is 0.89 micromolar, and compound 1 was itself found to be **not** useful clinically. Equally, all of the compounds in Friedlos identified as worth investigating further had IC50 values of 0.25 micromolar or below against cell line T79-A3. Compound 6 of Friedlos is therefore not potent against T79-

A3. Friedlos thus provides no disclosure or suggestion of any potent unsymmetric compound.

Indeed, the authors in Friedlos stated that compound 6 was "insufficiently potent to allow a full data set to be collected" (page 1272). This shows that, relative to the benchmark compound 1, already identified as **not** clinically useful, a compound with an IC50 of 3.4 against cell line T79-A3 was not considered by the Friedlos authors to be sufficiently potent to warrant further effort.

With such lack of potency, Friedlos fails to provide any suggestion which would have motivated a person skilled in the art to adopt unsymmetric compound 6 as a starting point for further experimentation, much less a starting point for a **two**-step structural modification to reach a compound of formula IIIb as now claimed. Again, a single substitution of a bromine for chlorine referred to in the Advisory Action would not result in or suggest a compound as now claimed. The statement in the Advisory that the person of ordinary skill in the art "would be invited to try the unsymmetric structure provided in compound 6 due to its potency against T79-A3, which could be further enhanced by changing the chlorine for bromine" entirely fails to recognize this two step structural modification, as well as the evident lack of potency of compound 6.

In contrast to compound 6, it is compound 13 of Friedlos which is the closest in structure to the compounds of formula IIIb of the invention. Compound 13 requires a single structural substitution of a mesylate for a bromine to result in a compound as now claimed. However, given the clear superiority of the compounds with a symmetric structure (as represented by active compounds 8, 9, 13 and 14) over the unsymmetric compound tested, Friedlos clearly leads towards persevering with **symmetric**

compounds and leads **away** from the asymmetric. Moreover, if there was ever any motivation to try substitution of a bromine in the structure of compound 13, it would **not** be to replace a bromine with a mesylate. There would have been no expectation by the skilled artisan that the result of such a substitution would be a drug with equal or improved activity. Given the statement by the Office that the person of ordinary skill in the art knows " that not only does using bromine create an active drug, but one that has greater activity than the chlorine substituted drugs", any move away from bromine to another substituent would be expected to **reduce** activity.

However, in complete contrast to this expectation, the unsymmetric bromomesylate compounds of the invention are more active than the compounds in Friedlos, including being more active than symmetric dibromo compound 13. To demonstrate this, attention is directed to the attached Rule 132 Declaration of William R. Wilson, a co-inventor and co-applicant (the Wilson declaration). The Wilson Declaration, discussed in detail during the interview, sets out IC50 data for all of the bromomesylate compounds the applicants have made and tested against the T78-1 and T79-A3 cell lines. The Wilson Declaration directly compares the results with compound 13 of Friedlos, the active compound structurally closest to the compounds of formula IIIb. The data reported for compound 13 is taken from Friedlos and is for a 24 hour drug exposure as compared to an 18 hour drug exposure for the compounds of formula IIIb. Applicants maintain that this comparison is valid, with the difference in exposure not biasing the comparison in favor of the bromomesylate compounds. If anything, the longer drug exposure in Friedlos favors compound 13 as the growth inhibition would be expected to increase with exposure.

Even with this decreased exposure, the results clearly show the markedly superior potency of the compounds now claimed. This superiority is particularly striking when compound 13 of Friedlos is compared to its equivalent bromomesylate, compound 27744, with the latter compound being approximately 39-fold more effective against the NTR-transfected cell line (IC50 of 0.19 for compound 13 compared to 0.0048 for compound 27744). This result is well beyond anything broadly equivalent or even a marginal improvement, and goes against any expectation of decreased activity due to replacement of a bromine. While the remaining comparisons between the other bromomesylate compounds are not as direct, it is clear that the same superiority is exhibited for the compounds of formula IIIb in general.

It is believed that this surprising showing of superior activity fully supports patentability of the present claims. The markedly superior effectiveness of the bromomesylate compounds of formula IIIb now claimed could not have been predicted from Friedlos, alone or in combination with Patani.

For all of the above reasons, it is believed that the invention as now claimed is patentably distinguished over Friedlos and Patani, either taken singly or in combination. Withdrawal of the obviousness rejection is respectfully requested.

DENNY et al
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Favorable action is awaited.

Respectfully submitted,

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